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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/266,803	03/12/1999	GREGORY M. GLENN	PM-256865	6258

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/18/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/266,803	Glenn et al.
Examiner	**Art Unit**
G.R. Ewoldt	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *12/31/01, 2/14/02, 3/01/02, and 7/18/02* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-35 and 50-107* is/are pending in the application.

4a) Of the above, claim(s) *30, 62-78, 104, and 107* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-29, 31-35, 50-61, 79-103, 105, and 106* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 25
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendments, filed 12/31/01 and 3/01/02, have been entered.

2. Applicant's election of Group I, Claims 1-29, 31-35, 50-61, 79-103 and 105-106, and the adjuvant species LT or a derivative thereof, with traverse, in Paper No. 29, filed 7/18/02, is acknowledged. Applicant argues that the examination of all claims would pose no undue search burden.

This is not found persuasive for the following reasons. While the inventions of Groups I and II may not be independent, they are distinct as defined by the MPEP § 802.01 as being "patentable over each other". MPEP § 803 further states that independent and distinct is to be considered independent *or* distinct for restriction purposes. Restriction between patentably distinct inventions can be proper even if said inventions are considered dependent, if undue search burden is established. Regarding search burden, the methods comprise different reagents, or combinations thereof, administered in different ways, thus, search burden has been established. However, upon further consideration, the species requirement has been withdrawn.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 30, 62-78, 104 and 107 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 1-29, 31-35, 50-61, 79-103 and 105-106 are being acted upon.

4. The Terminal Disclaimer, filed, 12/31/01, has been entered obviating the double patenting rejections over U.S. Patent No. 5,910,306.

5. Applicant is advised that the filing of corrected drawings may no longer be held in abeyance until such time as claims are found allowable. Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

New corrected drawings must be filed with the proper changes incorporated therein. See the PTO Form-948 mailed 12/07/00. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

Corrections other than Informalities Noted by Draftsperson on form PTO-948. All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

6. In view of Applicant's amendments and Remarks, filed 12/31/01 and 3/01/02, only the following rejections remain.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claim 3 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,340,588 (of record) or Paul et al. (of record) in view of Marinaro et al. (of record) and the admitted prior art on page 16 of the specification, for the reasons of record set forth in Papers No. 14 and 18, mailed 12/07/00 and 8/14/01, respectively.

9. Claim 3 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,340,588 (of record or Paul et al. (of record) in view of Kosecka et al. (of record), the admitted prior art on page 16 of the specification, and U.S. Patent No. 5,686,100 (of record) for the reasons of record set forth in Papers No. 14 and 18, mailed 12/07/00 and 8/14/01, respectively.

Applicant's arguments, filed 12/31/01, have been fully considered but have not been found persuasive. Applicant argues that the amending of the independent claims to recite an antigen that is not encapsulated, or to specifically recite that lipid vesicles are not being used, renders the claims nonobvious. It is noted, however, that Claim 3 recites a formulation comprising liposomes. It remains the Examiner's position that the inclusion of liposomes in the formulation of the claimed method renders the method obvious in view of the prior art, for the reasons of record.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 22-24 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, "toxin or a derivative thereof," (claims 22-24).

Applicant's arguments, filed 12/31/01, have been fully considered but have not been found persuasive. Applicant argues that the specification at page 17, line 2, supports the amended claims through the disclosure of "bAREs and a derivative thereof." Said generic disclosure is insufficient to support claims drawn to individual species. While the specification discloses several specific bAREs, e.g., CT, LT, DT, specific derivatives of the individual bAREs are not disclosed. Accordingly, the specification provides insufficient support for the methods of the amended claims.

12. The following are new grounds for rejection.

13. Claims 1-29, 31-35, 50-61, 79-103 and 105-106 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method of inducing an immune response comprising hydrating intact skin and applying a formulation to intact skin of an organism, wherein the formulation comprises at least one ADP-ribosylating exotoxin adjuvant and an effective amount of an antigen derived from a pathogen,

does not reasonably provide enablement for:

A) a method of inducing an immune response comprising:

applying a formulation to intact skin of an organism wherein the formulation comprises at least one adjuvant and an effective amount of an antigen derived from a pathogen,

activating a Langerhans cell, and

presenting at least one antigen or epitope thereof on a cell surface of the Langerhans cell to a lymphocyte (Claim 1).

B) a method of inducing an immune response comprising:

activating an antigen presenting cell, and

presenting at least one antigen or epitope thereof on a cell surface of an antigen presenting cell to a lymphocyte (Claim 32).

C) a method of inducing an immune response comprising:

activating a Langerhans cell,

signaling the Langerhans cell to migrate to a lymph node, and

presenting at least one antigen or epitope thereof on a cell surface of the dendritic cell to a lymphocyte (Claim 33).

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by

the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

Regarding the breadth of the claims, the specification the functionality of the claimed method employing *any* adjuvant must be considered highly unpredictable. As taught by the prior art, see for example Gupta et al., (1995, IDS), adjuvants function through at least three different classes of mechanisms: depot effects, delivery effects, and immunostimulatory effects. Given the unexpected nature of the undisclosed mechanism by which the instant invention functions, claims encompassing *all* adjuvants, functioning by entirely different mechanisms must be considered highly unpredictable. The aforementioned reference further teaches that even immunizations employing well-characterized adjuvants, administered through routine routes of administration, are not always effective, i.e., "Several adjuvants act with certain specific antigens and are not effective with other antigens." Note that the specification discloses exclusively the use of a group of closely related adjuvants referred to as ADP-ribosylating exotoxin adjuvant or bAREs on hydrated skin. No representative examples of other types of adjuvants are disclosed. Thus, the invention as broadly claimed must be considered highly unpredictable. Given said unpredictability, the method of the instant claims must be considered to require undue experimentation.

Further regarding the breadth of the claims, the claims assert specific aspects of a mechanism by which the claimed method might function, in particular, aspects involving antigen presentation and antigen presenting cells, particularly Langerhans cells. The specification, however, discloses just a single example (Example 17) describing an asserted interaction of the claimed method and Langerhans cells. The additional speculation at page 10 and Example 18 cannot be considered to add any demonstration of the mechanism of the method of the claims. As the specification also discloses that the functionality of the claimed method is somewhat unexpected:

> "Paul and Cvec (1995) stated that it is "impossible to immunize epicutaneously with simple peptide or protein solutions." Thus, transcutaneous immunization as described herein would not be expected to occur according to this group,"

claims reciting specific aspects of a mechanism by which the claimed method might function would require some specific demonstration of enablement.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of sufficient working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

14. Claims 1-29, 31-35, 50-61, 79-103 and 105-106 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed (note that the new matter portion of the claims in underlined), specifically:

A) an "antigen which is not encapsulated" (Claim 1),

B) the "method of Claim 1 wherein a physical, chemical, electrical, or sonic penetration enhancer is not used" (Claim 4),

C) the "method of Claim 1, wherein the formulation comprises a live or an attenuated live virus or virosome: and the antigen is expressed by the live or attenuated live virus or virosome, which is not encapsulated" (Claim 15),

D) "toxin or a derivative thereof," (Claims 25-26 and 85-90),

E) and at least some "antigen which is not encapsulated" (Claims 31 and 32),

F) and at least one "antigen derived from a pathogen which is not encapsulated" (Claim 33),

G) the method of claim 31, "wherein the formulation comprises a genetically produced derivative of ADP-ribosylating exotoxin in which ADP-ribosyl transferase activity is inactivated" (Claim 51),

H) the method of claim 31, "wherein the formulation comprises a chemically produced derivative of ADP-ribosylating exotoxin in which ADP-ribosyl transferase activity is inactivated" (Claim 51),

I) a method wherein the antigen/molecule "is at least partially purified" (Claims 54-60 and 96-102),

J) The method of Claim 1/31, "wherein at least one adjuvant is DNA from bacteria or containing unmethylated CpG motifs" (Claims 81 and 92),

K) The method of Claim 1/31, "wherein at least one adjuvant binds a receptor on antigen presenting cells" (Claims 82 and 93).

Applicant asserts in the amendments, filed 12/31/01 and 3/01/02, that no new matter has been added. However, upon careful review of the specification, insufficient support for the newly added limitations has been found. In some instances Applicant indicates specific passages, e.g., page 6, lines 10-11 and page 14, line 15, for amended Claim 15. Said passages do not however, support virosomes or non-encapsulated viruses.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 20 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the "ADP-ribosylating exotoxin" of the claims has no antecedent basis in Claim 1.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805 The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone numbers are 703-872-9306 (before final) and 703-872-9307 (after final).

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Patent Examiner
Technology Center 1600
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